Remarks

Claims 46 and 54 are amended herein to correct a minor typographical error.

New claims 88-89 are added herein. Support for new claims 88-89 can be found throughout the specification, such as on page 21, lines 22-28.

Applicants believe no new matter is added herein. Reconsideration of the subject application is respectfully requested.

Claim Rejections Under 35 U.S.C. 112, first paragraph

Claims 35, 46, 47, 54 and 60-87 are rejected under 35 U.S.C. 112, first paragraph, as allegedly not being enabled by the specification. Applicants respectfully disagree with this rejection.

The Office action confirms that the specification is enabling for a method of reducing the production of TNFα, MIP-2, IL-6 and KC induced by an immunostimulatory CpG oligodexoynucleotide (ODN) in a subject, and method for reducing the production of TNFα, MIP-2, IL-6 and KC induced by an immunostimulatory CpG ODN *in vitro*. However, the Office action alleges that the specification does not provide enablement for a method for reducing the production of TNFα, MIP-2, IL-6 and KC induced by any other means. Applicants respectfully disagree.

I. Wands Factors

At the outset, the Office action has agreed with the Applicants on the following points:

(A) *Breadth of claims:* The amended claims are directed to methods of reducing four cytokines (TNFα, MIP-2, IL-6 and KC) using suppressive ODNs that comprise the sequences of SEQ ID NO: 1 (claim 35), SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 46 and 54). These ODNs are at most 30 nucleotides in length, and have two to four guanonsine rich sequences and form a G-tetrad. Claims 60, 70-74 and 78 are limited to methods for reducing the expression of TNFα, MIP-2, IL-6 and KC wherein the ODN consists of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO:

17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21. Thus, the methods are limited to reducing ODNs have a specified sequence, length and physical characteristics.

(B) Nature of the invention: The claims are directed to methods of treatment that utilize nucleic acid sequences with a very specific sequence (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21), length (up to 30 nucleotides) and physical characteristics, to reduce expression of four specific cytokines, namely TNFα, MIP-2, IL-6 and KC. These ODNs can easily be produced by one of skill in the art.

(C) State of the prior art: The synthesis of ODNs, administration of ODNs to a subject of interest, and art-recognized models for testing therapies are well known in the art. In addition, methods for measuring TNFα, MIP-2, IL-6 and KC are well known in the art; kits to measure these cytokines are commercially available.

(D) Level of ordinary skill in the art: The level of ordinary skill in the art is of a molecular biologist and/or pulmonologist is high.

(E) Level of predictability in the art: Production of ODNs comprising the sequences set a specified nucleic acid sequence, and of a specified length is routine in the art. Further, there are methods, such as ELISAs (or ELISPOT) that are commercially available that can be used to measure cytokine production. There are art recognized models for inflammatory lung disease that can be used to test the effects of the ODNs of interest *in vivo*. These are also described in the specification. Exemplary results documenting the reduction in cytokine expression (induced by immunostimulatory CpG ODN) are provided in the specification (see, for example, pages 34-35).

(F) Amount of direction provided: The specification provides the sequences of the ODNs for use in the claimed methods (for example, Table 1, page 22). The specification further provides pharmaceutical compositions and methods of administration of ODNs (for example, page 24, line 9 to page 30, line 10) and methods for determining the effectiveness of an ODN, including methods for measuring cytokine or chemokine production (for example, page 30, line

11 to page 31, line 26; page 32, line 25 to page 34, line 16). The specification provides working examples wherein the claimed ODN reduce the production of TNFα, MIP-2, IL-6 and KC in vitro (RAW 246.7 cells) and in vivo (a mouse model of lung inflammation) wherein the inflammation is induced by immunostimulatory CpG ODN.

(G) Working examples: The specification provides the sequences of ODNs for use in the claimed methods and provides the use of an exemplary ODN (SEQ ID NO: 1) in inhibiting cytokine production *in vitro* (Example 2) and in an animal model of inflammation (Example 3).

However, the Office action alleges that because both of these model systems utilized immunostimulatory CpG ODN as the initiating agent for cytokine production, these examples do not enable the full scope of the claimed methods. The Office action asserts that "there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6 and KC administering **only** a suppressive oligonucleotide in vivo or in vitro" (emphasis added). The Office alleges that because the working examples utilized an immunostimulatory CpG ODN to induce inflammation, that the claims are enabled only for the administration of an immunostimulatory CpG ODN in conjunction with the ODN comprising the nucleic acid sequence set forth as SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21. Applicants respectfully disagree.

II. Evidence Presented in the Office Action, Correlation of the Working Examples with the Claims

Compliance with the enablement requirement does not require that a working example be disclosed (see MPEP § 2164.02). However, the present application provides more than one working example, including data obtained in vitro and data obtained in an art recognized system of pulmonary inflammation.

The Office action alleges that because both of these examples use immunostimulatory CpG ODN to induce inflammation, that the claims must be limited to using these ODNs. MPEP § 2164.02 states:

> The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. *To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.* (emphasis added).
>
> "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." (emphasis added)

Furthermore, MPEP § 2164.04 provides the basis for questioning the enablement provided in the specification for the presently claimed methods:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

As discussed above (see Section I), the present specification provides sufficient disclosure for one of skill in the art to make the ODNs comprising SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21. Furthermore, the Office action acknowledges that "Applicants have provided substantial evidence documenting showing that other ODNs from the group of SEQ ID NOs: 2-25 have subsequently been shown to be useful in reducing the production of cytokines, for example, Yamada et al. (J. Immunol. 169:5590-5594, 2002, of record shows that suppressive ODNs H154 and 1502 (Table 1 SEQ ID NOs: 1 and 20, respectively) inhibit production of IL-6, IL-12 and interferon-gamma (see e.g. Figures 1, 2 and 4, page 5591" (see page 5 of the Office action). The Office action also acknowledges the data presented in the Declaration of Dr. Gursel under 37 C.F.R. § 1.132 (submitted on June 18, 2010).

However, the Office action does not provide a single scientific reference or example from the specification to support the assertion that the results presented in the specification or the Declaration of Dr. Gursel cannot be extrapolated to inflammation induced by means other than immunostimulatory CpG ODN. Thus, the Office action has not provided "a reasonable basis to question enablement" (see MPEP § 2164.04). There is simply no evidence presented as to "why one would not expect to be able to extrapolate the [one] example across the entire scope of the claims" (see MPEP § 2164.02, second section).

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation (see MPEP § 2164.02). In fact, proof of enablement for other members of the claimed genus only is only required where adequate reasons are advanced by the U.S. PTO to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

In the present application, multiple working examples have been provided. Furthermore, additional examples were provided in the Declaration of Dr. Gursel. There is no evidence of record that establishes that the claimed methods could not be practiced by one of skill in the art. Thus, proof of enablement of the full scope of the claimed methods (inflammation induced by means other than CpG ODN) is simply not required.

Thus, the presently asserted rejection under 35 U.S.C. § 112, first paragraph is improper and should be withdrawn.

III. One of Skill in the Art Understands that the Claimed Methods Are Effective to Reduce Cytokine/Chemokine Secretion

In view of the evidence of record, one of skill in the art clearly would expect that the present methods would be effective to reduce cytokine and chemokine secretion induced by many means. Furthermore, there is sufficient disclosure provided in the specification, such that one of skill in the art could readily practice the claimed methods using the guidance provided in the specification.

However, in view of the (unsupported) allegation that the claimed methods would only be effective if immunostimulatory CpG ODNs were provided, the additional data is provided by the Applicants. Solely to advance prosecution, submitted herewith is a Declaration of Dr. Klinman under 37 C.F.R. § 1.132 (hereinafter "the Klinman Declaration"). The Klinman Declaration discloses that immunostimulatory CpG ODN mimic the immunostimulatory activity of bacterial DNA, and provides a scientific references (Exhibits A and B) that disclose that immunostimulatory CpG motifs act through Toll like receptor 9 (TLR9) and/or TLR7 to directly stimulate human B cells and plasmacytoid dendritic cells, promote the production of Th1 and proinflammatory cytokines, and trigger maturation of antigen presenting cells. Thus, immunostimulatory CpG ODN merely serve as a model agent that activates TLR9 and/or TLR7 and produce an inflammatory cascade. An anti-inflammatory agent that suppresses cytokine secretion induced by the biological pathway activated by these TLR receptors would suppress cytokine secretion. The means used to activate the TLR receptor would not alter the effect of the anti-inflammatory agent on the biological pathway. Thus, whether cytokine secretion was induced by immunostimulatory CpG ODN, bacterial DNA, or another means, oligodeoxynucleotide of 10 to 30 nucleotides in length that comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21 would have the same effect on cytokine/chemokine production. As disclosed in the Klinman Declaration, the biological action of a suppressive ODN does not result from the agent used to induce inflammation, but results from the biological mechanisms triggered through the TLR receptor.

Specifically, the Klinman Declaration (and accompanying Exhibit A) also provides evidence that a suppressive ODN A151 (SEQ ID NO: 2) suppresses inflammation induced by collagen and lippopolysaccaride. Furthermore, the Klinman Declaration (and accompanying Exhibit C) provides evidence that H154 (SEQ ID NO: 1, presently claimed) reduces the production of TNFα, MIP-2, IL-6 and KC induced by *bacterial DNA*. Thus, the Klinman Declaration provides evidence that the methods described in the specification are fully enabled, regardless of whether the agent that induces the inflammation is a CpG ODN, bacterial DNA, or another means.

Thus, the Klinman Declaration provides direct evidence that, one of skill in the art, using the general methods described in the specification, could use the ODNs comprising SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21 to reduce the production of TNFα, MIP-2, IL-6 and KC. Applicants submit that the specification is fully enabling for reducing the production of TNFα, MIP-2, IL-6 and KC induced by a variety of inducing agents. Contrary to the baseless assertions made in the Office action, the presently claimed methods are fully enabled by the specification.

IV. *The Scope of the Claims and the Scope of Enablement are Commensurate*

The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry (see MPEP § 2164.08). The first stage of inquiry is to determine how broad the claim is with respect to the disclosure. The present claims are directed to methods for reducing four cytokines (TNFα, MIP-2, IL-6 and KC) using suppressive ODNs that comprise specific sequences, namely SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21 wherein the ODNs are at most 30 nucleotides in length. The specification provides a complete description of the claimed methods, see for example, pages 24-32. The specification also provides working examples of reducing cytokine expression, specifically cytokine expression induced by immunostimulatory CpG ODN. However, MPEP § 2164.08 states "[l]imitations and examples in the specification do not generally limit what is covered by the claims." A Wands analysis has been provided (see above) that documents that the present specification, including the examples, is fully enabling for the claimed methods.

The second stage of inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. The Declaration of Dr. Klinman provides evidence that, using the guidance provided by the specification, one of skill in the art could readily use one of the specified suppressive ODNs to reduce cytokine expression. Thus, the present specification clearly teaches those skilled in the art how to make and use the claimed methods without undue experimentation.

Thus, the Applicants have demonstrated that the scope of the claims and the scope of enablement are commensurate.

In view of the arguments presented above, and the Declaration of Dr. Klinman, reconsideration and withdrawal of the rejection is respectfully requested.

Objection to the Specification and Declaration

The Office action objected to the specification because it discloses the use of both "RAW 246.7 cells and "RAW 264.7 cells," which appeared to be a typographical error. A review of the scientific literature suggests that there are two macrophage cell lines RAW264.7 and RAW246.7.

The specification is amended herein to clarify that RAW264.7 cell were used in the experiments described in Example 2.

The undersigned contacted Dr. Gursel and confirmed that he also used RAW264.7 cells in the experiments described in the Declaration under 37 C.F.R. § 1.132, submitted on June 18, 2010, but that he inadvertently called the cells "RAW246.7." Thus, the Declaration also includes a typographical error. However, Dr. Gursel confirmed the results and conclusions presented in the Declaration were correct, the only error is a typographical error in the name of the cells. Applicants believe no correction should be required. However, at the Examiner's request, a replacement Declaration will be prepared, executed by Dr. Gursel, and submitted to the U.S. PTO. The Examiner is respectfully requested to contact the undersigned by telephone if a replacement Declaration is required.

Conclusion

Applicants have made every effort to place the present application in condition for allowance. In the unlikely event that anything further is required before the allowance of all of the pending claims, Examiner Archie is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview with the supervisory Examiner present. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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